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Loss of MDC1 in Endometrial Carcinoma Is Associated With Loss of MRN Complex and MMR Deficiency

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Abstract. *Aim: To evaluate the frequency of loss of mediator of DNA damage checkpoint protein 1 (MDC1) protein expression in endometrial cancer (EC) and to determine whether loss of MDC1 is associated with certain clinicopathological parameters. Materials and Methods: MDC1 expression was examined in 426 samples of EC. The nuclear immunoreactivity of the protein was defined as: negative, weak moderate and strong. Results: Loss of MDC1 expression (defined as negative nuclear staining) was found in 8.9% (38/426) of ECs and was significantly associated with the loss of MRE11 homolog, double-strand break repair nuclease, RAD50 double-strand break repair protein and nibrin complex components. In addition, loss of expression of MDC1 showed a significant correlation with any mismatch repair deficiency, with endometrioid histological subtype and low tumour grading. Conclusion: Based on these findings, we suggest that MDC1 loss frequently occurs in ECs with microsatellite instability. Due to deficient homologous recombination DNA repair, MDC1-negative ECs might show an increased sensitivity to poly(ADP-ribose) polymerase-inhibitory therapy.*

Endometrial cancer (EC) is the most common gynecologic carcinoma in developed countries and the fourth most common neoplasm among women worldwide (1, 2). The vast majority presents at an early stage (75%) (3) with a relatively favourable prognosis (4). Treatment options, however, for advanced, recurrent or metastatic ECs, are limited and

consist mainly of cytotoxic chemotherapy. There are a large number of gene abnormalities as well as aberrant signaling pathways such as phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)/ phosphatase and tensin homolog (PTEN)/AKT serine/threonine kinase (AKT)/ mechanistic target of rapamycin kinase (mTOR) that appear to be promising targets but clinical studies are lacking. Recently, potential targeted treatments such as the immune checkpoint inhibitor pembrolizumab in patients with microsatellite instability (MSI)-high EC have been incorporated in clinical use (5, 6).

ECs are classified into two types based upon clinicopathological features and their clinical prognosis (7-9). Type I neoplasms are low-grade endometrioid ECs (10). They are stimulated by estrogens, patients present with them at an early stage and have a good prognosis (11). Endometrioid type accounts for the majority of ECs (90%) (12). Type II neoplasms are grade 3 endometrioid ECs and non-endometrioid tumours such as serous or clear cell carcinoma (12, 13). In addition, these two categories are characterized by their specific molecular aberrations which occur preferentially either in type I or type II ECs (9). Type I cancer harbours MSI as well as polymutations in different types of genes whereas *p53* mutations occur more common in type II ECs (14, 15).

Studies from the Cancer Genome Atlas classified 373 ECs into four genomic subtypes based upon their copy-number changes and genomic profile: DNA polymerase epsilon (*POLE*) ultramutated, MSI hypermutated, copy-number-low and the copy-number-high subgroups (16). The hypermutated subtype includes mostly endometrioid ECs, all harbouring MSI (16). These types of cancer are known to harbour mutations in other different genes (hypermutated genome) such as those participating in the DNA double-strand break repair mechanisms (17).

In the past few years, molecular-targeted cancer therapies have been developed, making use of the phenomenon of synthetic lethality (18). Nearly a hundred years ago, Bridges

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Key Words: MDC1, endometrial carcinoma, PARP, mismatch repair, targeted therapy.

first described the concept of synthetic lethality (19). Synthetic lethality between two genes arises when an alteration in the expression of either of them leads to a phenotype that is compatible with viability, whereas concurrent inhibition of both genes causes cell death (20). To implement this idea, cancers incorporating a synthetic lethal mutation have to be identified in order to target the synthetic lethal partner gene. One of the most beneficial features of such a specific anticancer drug is that it does not affect healthy tissue (21).

Recently, it was postulated that cancer cells which harbour deficiency of homologous recombination (HR) DNA-repair mechanisms have an increased sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors (22, 23). Inhibition of PARP1 enzymatic activity leads to an accumulation of single-strand breaks that are converted to double-strand breaks but cannot be repaired by HR. Inhibition of PARP has therefore been advanced as a novel targeted therapy for cancers harbouring breast cancer 1/2 (*BRCA1/2*) mutations (24). One of the most common mutations is found in the MRE11 homolog, double-strand break repair nuclease (MRE11), whose product is a part of the MRE11–RAD50 double-strand break repair protein (RAD50)–nibrin (NBN) (MRN) complex that is involved in the detection and repair of DNA double-strand breaks (25, 26). In a previous report we showed that not only the expression of MRE11 but also the expression of the other MRN complex components RAD50 and NBN is lost in 30.7% of ECs. Furthermore, we observed a significant association between loss of MRN components and mismatch repair (MMR) status in ECs. A decrease in MRE11 expression and function led to increased sensitivity towards PARP inhibition in EC cell lines (22). Recent studies have shown that mediator of DNA damage checkpoint protein 1 (MDC1) is a participant in the early response to DNA damage and its subsequent signaling within cells. Its co-localization with BRCA1 is suggestive of a role in homologous recombination.

MDC1 plays an important role in the DNA double-strand break repair machinery by being part of two important DNA repair pathways: the non-homologous end-joining response and HR (27, 28). The aim of the study was to evaluate the frequency of loss of MDC1 protein expression in ECs and to examine whether loss of MDC1 is associated with clinicopathological features and MMR protein status in EC.

Materials and Methods

EC sample characteristics. Tissue microarrays (TMAs) of formalin-fixed and paraffin-embedded ECs were assembled as previously published (22, 29), containing samples of two cohorts from the Institutes of Surgical Pathology, University Hospital Basel and Zurich (Switzerland), containing 339 (Basel-TMA) and 182 (Zurich-TMA) cancer samples in total. The study was approved for both cohorts by the local Scientific Ethics Committee (KEK-ZH-NR:

Table I. *Clinical characteristics of patients with endometrial carcinoma.*

Variable	n (%)
Age at diagnosis	
≤68 Years	218 (52.3)
>68 Years	199 (47.7)
Unknown	9 (2.1)
FIGO stage	
I	213 (50.0)
II	54 (12.7)
III	70 (16.4)
IV	14 (3.3)
Unknown	75 (17.6)
Histological subtype	
Endometrioid	355 (83.3)
Mucinous	3 (0.7)
Serous	31 (7.3)
Clear cell	14 (3.3)
Carcinosarcoma/MMMT	13 (3.1)
Undifferentiated	10 (2.3)
Endometrioid (incl. mucinous)	358 (84)
Non-endometrioid	68 (16)
Grading	
1 & 2	312 (73.2)
3	114 (26.8)

FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; MMT: malignant mixed Müllerian tumor.

2010-0358). In the present study, a total of 426 EC samples were available for further analysis due to tissue loss in some TMA spots. Clinical and pathological characteristics were taken from the clinical databases and pathology records. Routine hematoxylin and eosin sections were performed for histopathological evaluation. The stage of tumours was assessed according to the International Federation of Gynaecology and Obstetrics (FIGO) and TNM staging system. Histological subtype and tumour grade were defined according to the WHO classification 2014. Follow-up data are known from 480 patients. The median follow-up time was 31.5 (range=1-184) months for the Basel cohort, and 45 (range=1-124) months for the Zurich cohort. Baseline characteristics of patients with endometrial cancer are summarized in Table I.

Immunohistochemistry. After antigen retrieval, the slides were incubated with an antibody against MDC1 for 1 hour at room temperature. The antibodies against MDC1 (rabbit polyclonal, 1:250) were obtained from Bethyl Laboratories (Montgomery, TX, USA) and LubioScience (Zurich, Switzerland). The staining was conducted with a Ventana Benchmark automated system (Ventana Medical Systems, Tucson, AZ, USA) using Ventana reagents as well as UltraMap™ DAB detection kit (Ventana Medical Systems, Tucson, AZ, USA). The microscopic analysis of the staining was independently performed by two pathologists (SB, AN). We observed nuclear immunoreactivity of MDC1 and scored the intensity of nuclear expression as following: Negative, weak, moderate and strong. The protein expression of the MMR genes was considered as positive when nuclear staining was evident and negative when complete loss of nuclear staining was observed.

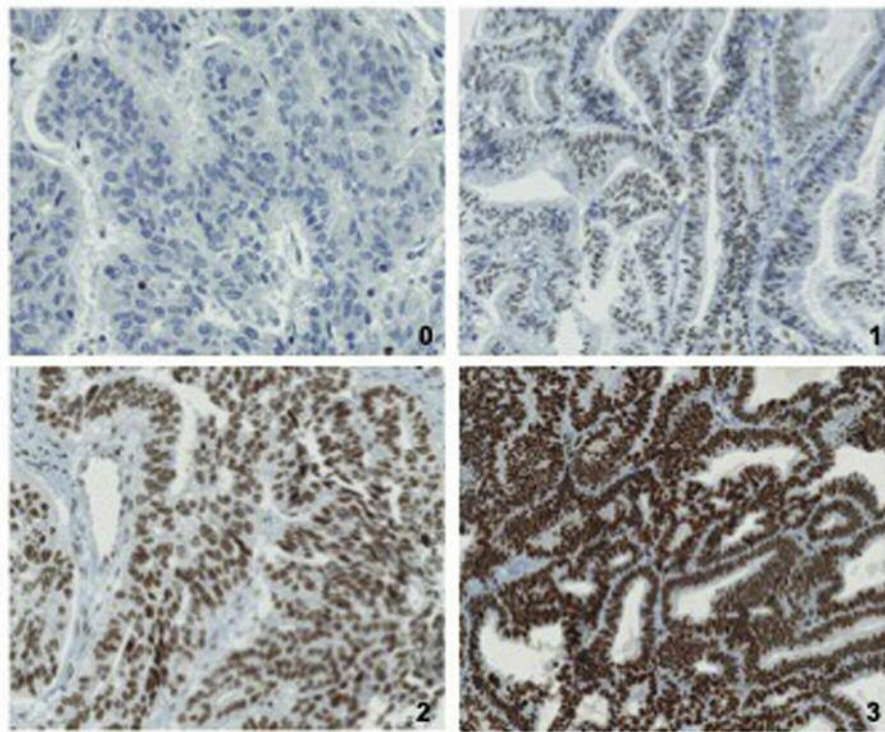


Figure 1. Expression of mediator of DNA damage checkpoint 1 (MDC1) protein in endometrial carcinomas as assessed by immunohistochemistry (magnification: $\times 20$). 0: Negative (complete loss of MDC1 protein expression). 1: Weak nuclear expression. 2: Moderate nuclear expression. 3: Strong nuclear expression. Representative images are shown.

Stromal cells showing nuclear staining were used as a positive control.

Statistical analysis. The statistical evaluation was performed with SPSS software Version 21.0 (IBM, Armonk, NY, USA). The scoring data of MDC1 were dichotomized into negative (no expression) and positive (any expression, weak to strong). The statistical significance of the association with MMR protein expression, MRE11, RAD50, and NBN, as well as clinicopathological parameters, was assessed by chi-squared test for trends and Fisher's exact test. Differences in survival curves were compared by the log-rank test. Generally, p -values of less than 0.05 were considered as significant.

Results

MDC1 protein expression. Immunohistochemical analysis of MDC1 of a total of 426 EC samples was performed. Representative images of the different expression patterns are shown in Figure 1. We found 38 negative cases, 85 weak positive, 203 moderate and 100 strong positive cases. The results were further grouped into negative and positive staining. A total of 388 (91.1%) EC samples showed positive staining for MDC1, 38 (8.9%) showed no nuclear immunoreactivity.

Association of MDC1 with clinicopathological characteristics. MDC1 negative cases were significantly associated with the endometrioid subtype (including mucinous) as compared with the non-endometrioid subtype (serous, clear-cell, carcinosarcoma and undifferentiated) ($p=0.018$) and occurred more often in grade 1 and 2 tumours than in grade 3 tumours ($p=0.02$) as shown in Table II. No association with FIGO stage or patient age was observed.

Association of MDC1 with MMR protein status and MRN complex proteins. In a previous study, we investigated MMR protein status mutL homolog 1 (MLH1), mutS homolog 2 (MSH2), mutS homolog 6 (MSH6), PMS1 homolog 2, mismatch repair system component (PMS2) and MRN complex proteins like MRE11, RAD50, and NBN in this EC cohort (22). Since MDC1 plays a role in DNA repair, we were interested in looking for an association between MDC1 and MMR, as well as MRN status. The expression of MMR proteins was considered as positive when nuclear staining was evident. Stromal cells showing nuclear staining were used as a positive control. MMR deficiency was defined as negative nuclear staining for any of the evaluated MMR proteins (MLH1, PMS2, MSH2 or MSH6). Negativity for

Table II. Immunohistochemical expression of mediator of DNA damage checkpoint 1 (MDC1), MRE11 homolog, double-strand break repair nuclease (MRE11), RAD50 double-strand break repair protein (RAD50), nibrin (NBN) mismatch-repair (MMR) proteins.

Marker	Expression	n (%)
MDC1 (n=426)	Negative	38 (8.9)
	Positive	388 (91.1)
MRN complex (n=414)	Negative	167 (40.3)
	Positive	247 (59.7)
MRE11 (n=415)	Negative	132 (31.8)
	Positive	283 (68.2)
RAD50 (n=419)	Negative	101 (24.1)
	Positive	318 (75.9)
NBN (n=416)	Negative	127 (30.5)
	Positive	289 (69.5)
Any MMR deficiency (n=391)	Negative	178 (45.5)
	Positive	213 (54.5)

MDC1 was more frequently observed in carcinomas with MMR deficiency (n=27, $p=0.0001$).

Furthermore, an association of carcinomas with negative MDC1 immunohistochemistry and loss of nuclear protein expression of the evaluated MRN complex proteins MRE11 (n=25, $p=0.0001$), RAD50 (n=16, $p=0.007$) and NBS1 (n=29, $p=0.0001$) were demonstrated (shown in Table III).

MDC1 expression and impact on overall survival in patients with ECs. In univariate Kaplan–Meier analysis, FIGO stage, histological subtype, grading and patient age were prognostic factors for overall survival (log-rank, $p<0.0001$ for all parameters). However, the expression of MDC1 (log rank, $p=0.110$) was not associated with overall survival.

Discussion

Cells are continuously exposed to agents that lead to DNA damage, which, if not repaired effectively and efficiently, can result in genomic instability. The HR pathway plays an important role in this context. HR-deficient tumours have been reported widely in literature, including ovarian and breast cancer (30, 31).

In mice, mutation of *Mdc1* causes impaired spermatogenesis, as well as other disorders due to genomic instability (32). Because of its role as a potential tumour suppressor, loss of MDC1 expression has been described in various types of neoplasms such as breast, lung (33) and gastric carcinoma (34). Besides being part of HR (14, 15), MDC1 contributes to the DNA damage-response pathway by managing the activation of the intra-S-phase and G₂/M phase cell-cycle checkpoints in the case of DNA damage (35, 36). After exposure of cells to ionizing radiation and other factors as UV irradiation and

Table III. Association of expression of mediator of DNA damage checkpoint 1 (MDC1) with clinicopathological features, and components of the MRE11 homolog, double-strand break repair nuclease (MRE11)–RAD50 double-strand break repair protein (RAD50)–nibrin (NBN) (MRN) complex.

Variable	MDC1, n		p-Value
	Negative	Positive	
Histological subtype			
Endometrioid	37	318	0.25
Mucinous	0	3	
Serous	0	31	
Clear cell	1	13	0.018
Carcinosarcoma/MMMT	0	13	
Undifferentiated	0	10	
Endometrioid (incl. mucinous)	37	321	
Non-endometrioid	1	67	
Grade			
1 & 2	34	278	0.02
3	4	110	
Any MMR deficiency			
Negative	27	151	<0.0001
Positive	10	203	
MRE11			
Negative	25	107	<0.0001
Positive	11	272	
RAD50			
Negative	16	85	0.007
Positive	20	298	
NBN			
Negative	29	98	<0.0001
Positive	7	282	
MRN complex			
Negative	30	137	<0.0001
Positive	6	241	

MMMT: Malignant mixed Müllerian tumor; MMR: mismatch repair.

endogenous damage, MDC1 mediates the recruitment of several DNA-repair proteins to the site of damaged DNA. These DNA damage-induced foci involve other important proteins such as tumour protein p53 binding protein 1 (TP53BP1), BRCA1 and the heterotrimeric MRN complex (37).

To our knowledge, this is the first report to show the role of MDC1 protein in samples of human EC. Our studies show that the expression of MDC1 protein is lost in a notable proportion of ECs (8.9%). In a previous study, we investigated the MMR protein status (MLH1, MSH2, MSH6, PMS2) and MRN complex proteins MRE11, RAD50, and NBS in this EC cohort (22). Since MDC1 plays a role in DNA repair, we were interested in an association between MDC1 and MMR, as well as MRN status. We observed an association between loss of MDC1 and MMR protein deficiency as well as loss of nuclear protein expression of the evaluated MRN complex proteins which suggests that

MDC1 loss is a frequent occurrence in MMR-deficient ECs (hypermutated subgroup).

Previous studies verified that tumour cells with impaired HR DNA-repair exhibit increased sensitivity to PARP inhibitors. The therapeutic benefit of PARP inhibitors in germline BRCA1/2-deficient tumours, such as breast, ovarian, pancreatic and prostate cancers has been proven *in vitro* as well as in clinical trials (38-41). For EC, the synthetic lethal interaction between MRE11 and PARP1, was demonstrated *in vitro* with PARP inhibitors (22). Furthermore, the loss of PTEN, which is the most commonly affected gene in endometrioid ECs (42), sensitizes cancer cell lines to PARP-inhibitory treatment (43) although the exact function of PTEN in homologous recombination is not clearly defined. Various studies have suggested that loss of MDC1 might be associated with a favourable prognosis. Recently, Wang *et al.* showed that MDC1-depletion combined with PARP inhibition can enhance the sensitivity of olaparib in nasopharyngeal carcinoma. MDC1-deficient cells also revealed a decrease of BRCA1, BRCA2 and RAD51, which is suggestive of a direct inhibit of HR-mediated DNS repair through impairment of neighboring foci. The down-regulation of MDC1 led to defective HR through blockage of DNA damage-repair proteins (44).

Based on these findings, we conclude that loss of MDC1 expression occurs in a notable proportion of ECs, is more common in low-grade endometrioid EC than in non-endometrioid EC, and is associated with MMR deficiency. Due to deficient HR DNA repair, we postulate that tumours with loss of MDC1 might have increased sensitivity to PARP inhibitor therapy. The effect of MDC1-negative ECs on sensitivity to PARP inhibitor in EC has not yet been proven and needs further investigation.

Conflicts of Interest

The Authors declare that no conflict of interest exists in regard to this study.

Authors' Contributions

Conceived and designed the experiments: KJD SB. Performed the experiments: SB AN. Analyzed the data: SB AN KJD EPS DM. Contributed reagents/materials/analysis tools: SB AN KJD. Wrote the article: DM, BN, EPS, KJD SB AN.

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